New routes to the functionalisation patterning and manufacture of graphene-based materials for biomedical applications

A De Sanctis, S Russo, M F Craciun, A Alexeev, M D Barnes, V K Nagareddy and C D Wright*

Centre for Graphene Science, College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter EX4 4QF, United Kingdom

*Author for correspondence:
C David Wright
e-mail: david.wright@exeter.ac.uk

Abstract

Graphene-based materials are being widely explored for a range of biomedical applications, from targeted drug delivery to biosensing, bioimaging and use for antibacterial treatments, to name but a few. In many such applications it is not graphene itself that is used as the active agent, but one of its chemically-functionalised forms. The type of chemical species used for functionalisation will play a key role in determining the utility of any graphene-based device in any particular biomedical application, since this determines to a large part its physical, chemical, electrical and optical interactions. However, other factors will also be important in determining the eventual uptake of graphene-based biomedical technologies, in particular the ease and cost of manufacture of proposed device and system designs. In this work we describe three novel routes for the chemical functionalisation of graphene using oxygen, iron chloride and fluorine. We also introduce novel in-situ methods for controlling and patterning such functionalisation on the micro- and nano-scales. Our approaches are readily transferable to large-scale manufacturing, potentially paving the way for the eventual cost-effective production of functionalised graphene-based materials, devices and systems for a range of important biomedical applications.

1. Introduction

The biomedical applications of graphene-based materials are wide-ranging and potentially of much importance and impact, spanning, for example, drug delivery, photothermal therapy, tissue engineering, bactericides, biosensing and bioimaging [1]. Such wide-ranging applicability of graphene arises from its unique physical, electrical, mechanical and chemical properties, in particular its high surface area, excellent electrical and thermal conductivity, optical transparency, biocompatibility and, importantly, its ease of functionalisation. Indeed, for many biomedical applications it is not graphene *per se* that is used as the active material, but rather a functionalised form of graphene, where functionalisation with particular chemical species has been carried out in order to enhance performance and increase selectivity (e.g. to a particular reaction). One of the most widely used functional groups is simple oxygen, which yields of course graphene oxide, or GO. For example GO (and reduced-GO) has been used extensively for drug delivery in cancer treatment (see e.g. [2-4]), for the fabrication of biosensing platforms capable of detecting the presence of key disease biomarkers and DNA sequences (see e.g. [5-7]), for the in-situ bioimaging of cells [8], as well as finding application as a most effective antibacterial agent (see e.g [9-11]). Oxygen is however not the only useful species for graphene functionalisation, far from it. We ourselves, for example, have shown that functionalisation of few-layer graphene (FLG) with iron chloride ($FeCl_3$) leads to exceptional photoelectrical properties [12] that can be exploited in a wide variety of applications, including highly sensitive and high-resolution photodetectors for biosensing and bioimaging. Fluorine-functionalised graphene has also been shown to possess very useful biomedical applications, particularly for the detection of various analytes and biomarkers [13], and may ultimately find application in the the management and detection of a range of important and widespread health problems, such as diabetes and cardiovascular disease.

In this study we report on the functionalisation of graphene using the three chemical species introduced above, namely oxygen, iron chloride and fluorine. In particular we report on novel ways for localising such functionalisation, potentially down to the nanoscale. The ability to exert local control of the functionalisation process and to pattern functionalised regions as desired in a simple and effective way, which we demonstrate here, should make for more straightforward and cost-effective production of future graphene-based biomedical devices.

2. New routes to oxygen-functionalised graphene devices

The efficient and cost-effective production of functionalised graphene devices is still hampered somewhat by conventional approaches to device fabrication. Such conventional approaches involve several process steps including graphene deposition, graphene film transfer, graphene functionalisation, ex-situ lithographic patterning and metal contact deposition; processes that are time consuming, not always reproducible and potentially deleterious to the properties of the CVD-graphene layer itself (see e.g. [14-16]). An alternative approach that avoids many such drawbacks is to carry out in-situ plasma functionalization and in-situ lithographic patterning of large-area CVD graphene directly on the copper substrates used in the graphene deposition process. This enables the fabrication of devices in their entirety prior to any transfer steps. Here we concentrate on the production of oxygen (plasma) functionalised graphene materials and devices which, as discussed in the introduction above, have found widespread application in the biomedical field.

The plasma oxidation method for the production of graphene oxide has several advantages *cf*. the more commonly used liquid-phase approaches (such as the Hummer's method). In particular, plasma-oxidation does not contaminate samples with by-products of (wet) chemical reactions [17, 18], it is easily scaled in size, it is relatively environment-friendly and involves fewer stages as compared to conventional methods [19]. Moreover, patterned graphene/graphene oxide structures and devices can also be readily created using plasma modification of graphene combined with lithographic processing, and this can all be carried out prior to the transfer, onto the desired substrate, of the (functionalised and patterned) graphene from its CVD (catalytic) Cu foils. In this way complex micro- and nano-scale GO device structures can be reliably fabricated in fewer steps than via conventional approaches and, importantly, be readily transferred onto a range of target surfaces including rigid and flexible substrates, biocompatible substrates and even textiles (for, e.g. wearable biomedical devices).

Our novel fabrication process is illustrated in figure 1, here using an 80 x 80 µm GO logo (a G surrounded by an O) by way of demonstration (and in which the G and O regions are plasma-oxidised while the remainder of the film remains as graphene). In detail the our process consists the following: first, a 200 nm thick layer of positive e-beam resist (PMMA) is spin coated onto graphene film on copper foil, as grown by the CVD method; next, the area to be functionalised is exposed by e-beam and subsequently developed, leaving the unmasked regions of the graphene film exposed; next the sample is exposed to the oxygen plasma; then, the copper substrate is etched away from the underside using ammonium persulphate solution; the PMMA-graphene stack is cleaned multiple times in de-ionized water and then transferred onto the target substrate; finally, the PMMA mask is removed using acetone and the sample is cleaned with isopropyl alcohol. To verify that the G and O patterned regions, and only those regions, were successfully oxidised, we carried out Raman mapping of the sample (with a 1 µm step size) and plot, in figure 1*g*, the ratio of the intensities of the Raman D and G peaks (I_D/I_G). It can be seen that a striking I_D/I_G contrast exists between the oxidised regions and those that were protected from the plasma, indicating successful oxidation of the desired regions. The oxidized 'GO logo' pattern of figure 1*g* can also be clearly seen via SEM imaging, as shown in figure 1*h*, the darker regions in that image indicating a reduction of the conductivity of the plasma exposed area.

Although we have here shown the production of a simple logo to demonstrate on the micron-scale the effective local functionalisation of graphene (to graphene oxide), it is straightforward to use the technique we have presented to fabricate entire devices with features down to the nanoscale if desired. For example, we have previously successfully produced a flexible and transparent plasma functionalised graphene/graphene oxide humidity sensor that outperformed high-grade commercial humidity sensors [20]. The production of biomedical-oriented devices using our technique is also entirely feasible and could prove particularly beneficial in the biosensing area. Moreover, while we in this section have concentrated on oxygen plasma functionalisation, the approach described is generic and can undoubtedly be applied in the case of functionalisation by other chemical species.

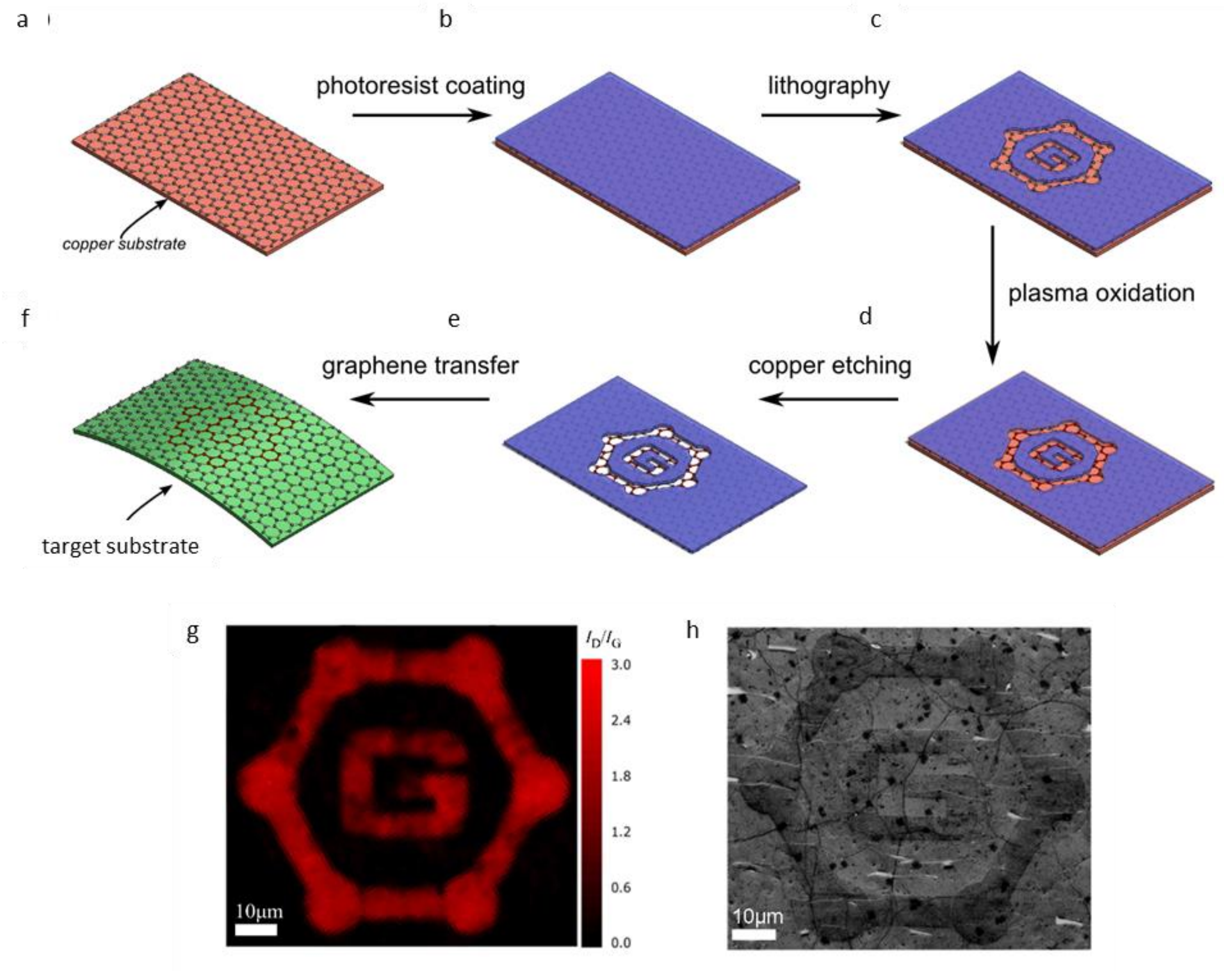

Figure 1. Schematic representation of the in-situ functionalisation (here using oxygen) and patterning of as-grown CVD graphene: (*a*) to (*b*) photoresist (PMMA) coating of as-grown CVD graphene; (*b*) to (*c*) e-beam lithography on Cu; (*c*) to (*d*) plasma oxidation (in a reactive ion etching system); (*d*) to (*e*) copper etching in APS solution; (*e*) to (*f*) graphene transfer onto the target (here shown as a flexible) substrate. (*g*) and (*h*) show a Raman I_D/I_G map and SEM image of the final 80 x 80 µm GO logo [Adapted and reprinted with permission from [20]; Copyright IoP 2016]

3. New routes to patterning $FeCl_3$-functionalised graphene for high-definition bioimaging and biosensing

Optoelectronic biosensing platforms are attracting growing interest as they can potentially be incorporated in portable medical devices to be used in a multiplicity of environments [21]. In general, such platforms are based on a light source, a reactive medium and a photodetector with spectral selectivity. Thus, photodetectors for high-definition sensing and imaging and able to operate in various spectral ranges are needed. In particular, infrared (IR) and near infrared (NIR) detectors have applications in biochemical detection and functional-NIR medical imaging. On the other hand, ultraviolet (UV) light is strongly absorbed by many materials, enabling the observation of characteristics that are difficult to detect by other methods. For example, UV imaging is an emerging inspection method for microbial contamination of food products. Several alternative approaches for optoelectronic biosensing have been demonstrated in recent years based, for example, on plasmonic nano-resonators [22], optofluidic devices [23] or integrated semiconductor photodetectors [24, 25]. However, the push for the development of low-cost, flexible and wearable devices [26] has instigated the exploration of novel materials, amongst which is graphene [27,28] and its functionalised forms.

While in the previous section we concentrated on oxygen functionalisation, we now turn our attention to the functionalisation of few-layer graphene with $FeCl_3$. This results in the best transparent electrical conductor currently available [12], and one that outperforms indium tin oxide (ITO) as currently used extensively in touch screen displays etc. However, $FeCl_3$ functionalised graphene is much more than just a high-performance transparent conductor, it offers a gamut of exciting properties and potential for various applications. Examples include an unforeseen stability to harsh environmental conditions [29], ease of large-area processing [30], the realisation of all-graphene photodetectors [31] and the potential to enhance the efficiency of photovoltaic and organic light emitting devices [30, 32]. When used as a transparent electrode in electroluminescent devices, $FeCl_3$ functionalised graphene also increases the brightness of the emitted light by up to 50% as compared to pristine graphene, and up to 30% compared to state-of-the-art commercial electrodes [33]. Furthermore, the record high charge density achieved in $FeCl_3$ functionalised graphene [12, 34] makes it an attractive platform for the production of high-responsivity, high-resolution photodetectors.

Graphene-enabled high resolution imaging could open a new era in small-footprint high-performance biosensing devices. However, the scientific community is presently facing difficult challenges in realising such devices. In particular, efficient nano-scale graphene photodetectors are presently not possible due to the dominance of photo-thermoelectric effects (PTE) in graphene, which sets the minimum size for a graphene pixel to the tens of micron scale (as demonstrated by several pioneering works [35-39]). Another obstacle is imposed by the diffraction limit, setting a further constraint on the (minimum) size of devices. Furthermore, the electrical and optical properties of graphene are severely hampered by contamination of the material in ambient conditions, requiring elaborate ways of encapsulation to preserve the properties of graphene, so limiting its use in realistic situations [40].

Many of the above issues have been recently tackled using $FeCl_3$-intercalated few-layer graphene [12, 29-34] ($FeCl_3$-FLG), together with a new way to define optically active junctions [41]. As shown in figure 2*a*, a laser beam is used to control the microscopic arrangement of $FeCl_3$ molecules which are intercalated between sheets of graphene, in order to define photoresponsive junctions. This approach enables conceptually new ways to capture and manipulate light beyond conventional plasmonic structures. Intercalation of graphene with $FeCl_3$ results in a strong charge-transfer [12, 30] and consequent p-type doping of the graphene. By selectively removing $FeCl_3$ molecules, therefore, a p-p' junction can be defined, as shown in figure 2*b*, (where the total charge concentration in the graphene stack is shown before and after laser-irradiation of a strip across the sample [30, 42]). Such a junction shows a strong photoresponse, as shown by the scanning-photocurrent maps in figure 2*c*. By analysing the direction of the observed photocurrent and calculating the different contributions to the photocurrent arising from the PTE and photovoltaic (PV) effects, it is shown that in $FeCl_3$-intercalated graphene strong quenching of PTE effects is possible and the photoresponse is dominated by the PV effect [41].

The quenching of the PTE effect in $FeCl_3$-FLG removes one of the key limitations, in terms of device-scaling and hence sensing and imaging resolution, of graphene-only photodetectors. Indeed, the quenching of the PTE effect in $FeCl_3$-FLG allows the definition of photoactive junctions in a much more confined space. To this end, emerging nano-photonics near-field techniques [43] can be used in order to surpass the other 'block' on high-resolution sensing and imaging, namely the diffraction limit. For example, in figure 2*d* and 2*e* a red (λ= 632 nm) laser focused onto a metallic atomic-force microscope AFM tip is used to define a photoactive p-p' junction with a peak-to-peak distance of only 250 nm, less than half the laser wavelength used. The broad spectral response of graphene is also maintained in these sub-diffraction $FeCl_3$-FLG devices, which show a consistent proportionality between optical response and photon energy from the ultraviolet (UV) right through to mid-infrared (MIR) wavelengths. Another extraordinary characteristic of laser patterned $FeCl_3$-FLG junctions is their linear dynamic range (LDR). This parameter determines the range of power densities over which a photodetector's response is linear. In graphene such linearity is limited by the aforementioned PTE effect and the small density of states (DOS) available for photoexcitation. In $FeCl_3$-FLG, instead, a LDR of 44 dB is observed. This is a remarkable 4500 times larger than any other graphene-based photodetector reported to date [41].

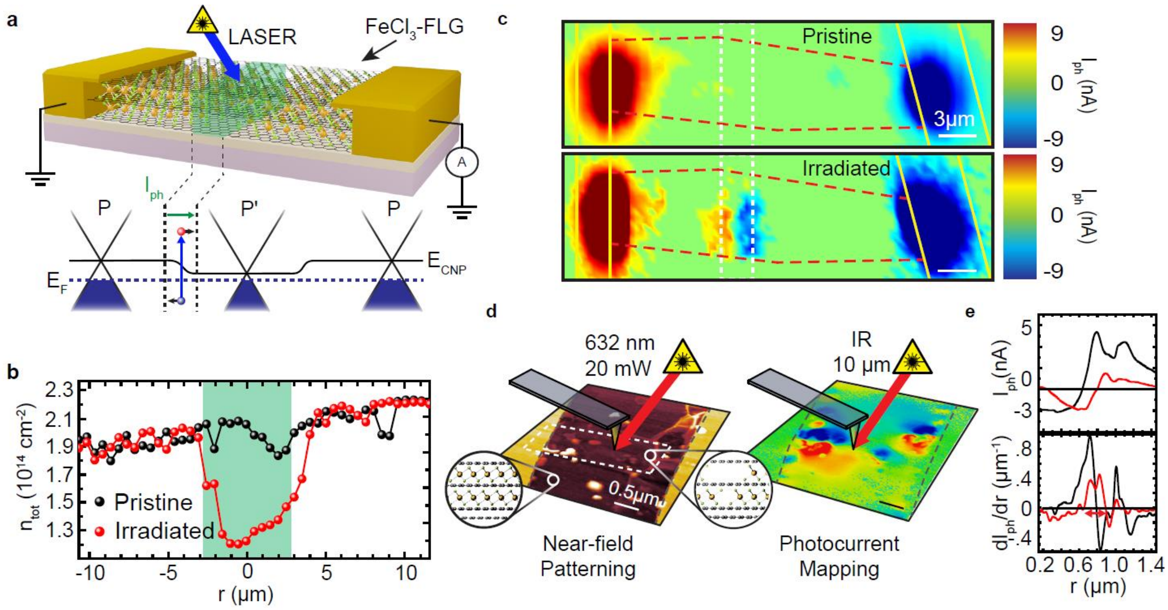

Figure 2: Laser-written photodetectors in FeCl3-intercalated graphene. (*a*) Device structure and scanning photocurrent measurement configuration (top) of a p-p'-p junction. The selective displacement of $FeCl_3$ molecules with laser light allows the formation of a p region (in green). The schematic band structure (bottom) of each region illustrates how photo-generated carriers drift under the induced chemical potential gradient. (*b*) Total charge carrier concentration in pristine and laser-irradiated $FeCl_3$-FLG. (*c*) Scanning photo-current maps of a FeCl3-FLG flake (red-dashed lines) with Au contacts (yellow lines) before and after laser-assisted displacement of $FeCl_3$ (white-dashed lines). (*d*) Near-field patterning of photoactive junctions in $FeCl_3$-FLG. AFM topography (left) and scanning photocurrent map (right) of the flake after laser irradiation by a λ= 632nm laser (white dashed lines). Insets: illustrations of the chemical structure in p- and p-doped regions. (*e*), Line scans of photocurrent measured across the laser defined p-p'-p junctions. Bottom panel shows first derivative plots of the photocurrent signal, indicating a peak-to-peak distance of only 250 nm between adjacent junctions. [Adapted and reprinted with permission from [41]; copyright AAAS 2017]

To summarise, by using $FeCl_3$ functionalisation of graphene we can 'engineer' the hot carrier photoresponse so as to enhance both pixel resolution and linear dynamic range, whilst at the same time maintaining a broad spectral response, in atomically thin devices and systems. Such capabilities could have potentially wide-reaching impacts on technologies for spectroscopy, high definition bioimaging and biosensing. We might see their use in, for example, disposable medical diagnostic tools for the detection of biofluorescent molecules with sub-wavelength resolution [44], or in skin-conformable photodetectors for heart rate measurements (known as photoplethysmography), or perhaps wearable and elastic UV cameras for minimally-invasive probes and UV tracking.

4. Nano-patterning of fluorine-functionalised graphene for biosensing

Yet another biologically-useful functionalisation of graphene is that using fluorine. In fluorinated graphene, fluorine adatoms are covalently bonded to the carbon atoms and, owing to the high electronegativity of the bound fluorine, FG benefits from an augmented sensing performance for various analytes and biomarkers [45]. Previous studies have also revealed that sensing activity strongly depends on the fluorine content [46]; the interactions between FG and biomolecules can be drastically modified by varying the amount of fluorine functionalisation. Hence controlling and tuning the fluorine content are important aspects for the further development of FG-based biosensors. In particular, the possibility to control locally the fluorine content would enable a new concept of biosensing applications whereby a wide variety of biomolecules can be detected at different positions on the same sensor by patterning the degree of functionalisation.

We have shown that such local control of fluorination can be achieved by starting off from a highly fluorinated graphene sheet and reducing the level of functionalisation in specific regions by irradiation with an electron beam [47, 48]. This approach is summarised in figure 3. The starting material is a sheet of functionalised graphene obtained by exposure to F_2 gas at 450^{o}C, resulting in a fluorine content of 28%. Subsequently, irradiation of the functionalised graphene with an electron beam with appropriate energy dissociates the C–F bonds, so reducing the level of fluorination. This innovative technique offers a simple and direct way to pattern spatially, on the nano-scale, the degree of fluorination. This has also been experimentally confirmed by the demonstration that the value of the energy gap of fluorinated graphene depends on the F content. As shown in figure 3*d*, a transition from a semiconductor (i.e. FG) to a semi-metal (i.e. graphene) was experimentally observed upon changing *in-situ* the F-coverage from 28% to <1% using electron beam irradiation. A significant change in the resistivity of FG has been shown to accompany this transition. It was found that the relative decrease in resistance per square upon electron-irradiation of micro-structures is at least seven orders of magnitude from 1TΩ to 100 kΩ. Furthermore, our process can be used for patterning different surface areas ranging from few tens of squared micrometres to channels just a few tens of nanometres wide (dependent on e-beam resolution).

In summary, the patterning of fluorine-functionalisation content in FG by means of electron beam irradiation offers novel avenues for biosensing. Sensing of various biological analytes has already been demonstrated using fluorinated graphene where the F content was varied. The implementation of FG biosensors where F content is tuned by electron beam patterning to different values across the same device would enable a new multi-functional biosensors whereby a wide variety of biomolecules can be detected in a single device, perhaps for the monitoring of biologically important analytes such as those needed for the management of diabetes and cardiovascular diseases (i.e. glucose, cholesterol, triglyceride, glycated haemoglobin).

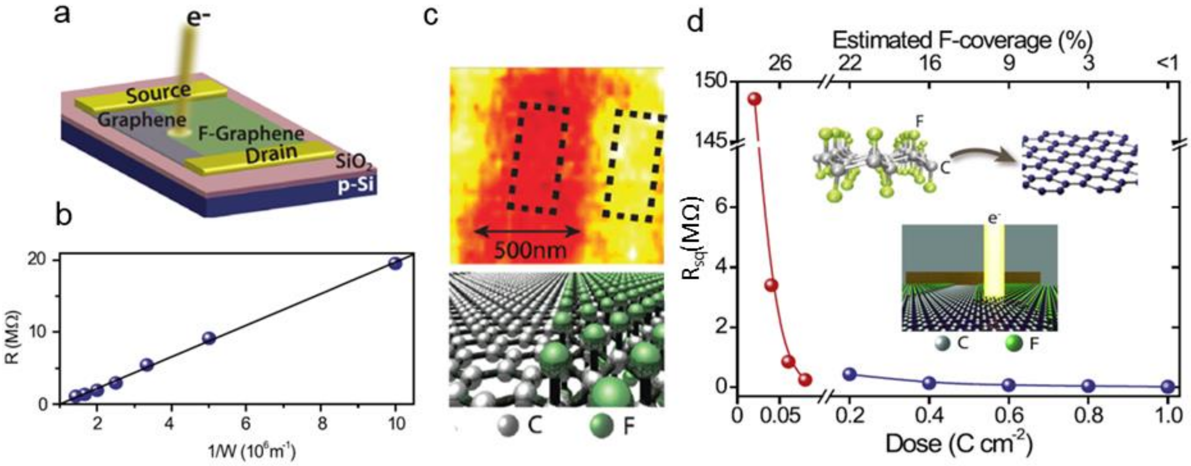

Figure 3. Nano-patterning fluorinated graphene. (*a*) Schematic illustration of the device configuration under irradiation with a beam of electrons. The fluorinated graphene (green) is reduced to graphene (grey) upon electron irradiation. (*b*) the sample resistance plotted against inverse width W for a device. The continuous line is a linear fit. (*c*) topographical AFM image for the unexposed (orange) and exposed (red) fluorinated graphene. The bottom panel illustrates the crystal structure of pristine graphene (gray) and fluorinated graphene (green). [Reprinted with permission from [47]; copyright American Chemical Society 2011]. (*d*) Graph of the measured zero-bias square resistance (Rsq) at room temperature after subsequent steps of electron assisted defluorination conducted on the same sample. The insets show the process of electron-assisted defluorination where fluorinated graphene (left structure with carbon atoms in grey and fluorine atoms in green) is reduced to graphene (right structure). [Reprinted with permission from [48]; copyright DPG/IoP 2013]

Authors' contributions. All authors contributed significantly to this work. AdeS, SR, MFC and CDW wrote the paper. SR, MFC and CDW led the work.

Competing interests. We declare we have no competing interests.

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